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RESEARCH ARTICLE

Life's Essential 8 and midlife trajectories in cognition and brain health: The CARDIA study

Christina Silvia Dintica[1] | **Xiaqing Jiang**[1] | **Lenore J. Launer**[2] | **R. Nick Bryan**[3] | **Kristine Yaffe**[1]

[1]Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, California, USA

[2]National Institute on Aging, National Institutes of Health, LEPS/IRP/NIA/NIH, Laboratory of Epidemiology and Population Sciences, Baltimore, Maryland, USA

[3]Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA

Correspondence
Christina Dintica, Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, CA 94122, USA.
Email: Christina.dintica@ucsf.edu

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Abstract

INTRODUCTION: Poor cardiovascular health (CVH) is linked to Alzheimer's disease and dementia; however, its association with neurocognitive trajectories earlier in life remains underexplored.

METHODS: We included 3224 participants with information on CVH at early midlife (mean age 45.0 ± standard deviation 3.4) an cognitive assessments, and neuroimaging 5, 10, and 15 years later including white matter hyperintensities (WMHs), total gray matter (GM), and hippocampal volume. CVH was operationalized according to the American Heart Association's (AHA) "Life's Essential 8" (LE8) guidelines. The association between LE8 and cognitive and neuroimaging measures was examined using mixed linear regression adjusting for age, sex, race, and education.

RESULTS: Worse LE8 score was associated with steeper decline in cognition, higher accumulation of WMHs, and steeper decline in total GM and hippocampal volume.

DISCUSSION: Poor CVH is related to accelerated brain aging across midlife, highlighting the need to screen for and improve CVH earlier to prevent adverse cognitive outcomes.

KEYWORDS
cardiovascular, cognition, cohort study, longitudinal, magnetic resonance imaging, midlife, neuroimaging

Highlights

- Poor cardiovascular health in early midlife is associated with faster decline in cognition across 10 years overall and in specific domains.
- Poor and intermediate cardiovascular health was associated with higher accumulation of white matter hyperintensities across midlife.
- Poor cardiovascular health was associated with faster atrophy in total gray matter volume and hippocampal volume.

1 | INTRODUCTION

Given the rapid increase in the prevalence of dementia and limited effective treatments, dementia remains a significant global challenge for public health and social care.[1] This underscores the importance of addressing modifiable risk factors as primary or adjunctive interventions to reduce the risk of dementia and maintain cognitive function.[2,3] There is growing evidence suggesting that cardiovascular risk factors play an important role in risk of cognitive decline and development of dementia.[3–6] However, most studies have been conducted on participants in late life. Yet, emerging evidence suggests cardiovascular health (CVH) is important earlier in the life course and secular trends highlight earlier and increasing cardiovascular risk factor prevalence such as obesity and diabetes even in childhood.[7]

The American Heart Association (AHA) introduced the Life's Simple 7 (LS7) score in 2010, defining ideal CVH based on seven health factors:[8] smoking, body mass index (BMI), physical activity, diet, cholesterol, blood pressure, and fasting blood glucose. Several longitudinal studies have investigated the relationship between LS7 and dementia in American cohorts[9–11] and some European cohorts,[12] but there has been sparse investigation on whether CVH is associated with brain health earlier in life. Recently, the AHA introduced an enhanced approach called "Life's Essential 8" (LE8), which provides a more comprehensive and sensitive assessment of CVH and expanded to include sleep.[13,14]

As part of the ongoing Coronary Artery Risk Development in Young Adults (CARDIA) Study, we sought to investigate the associations of the comprehensive LE8 score with changes in cognitive function and brain structural magnetic resonance imaging (MRI) measures across early to late mid-life. We hypothesized that having a poor LE8 score would be associated with an accelerated cognitive decline, as well as an accelerated decline in gray matter (GM) volume, and a higher rate of white matter hyperintensities (WMHs) accumulation. This investigation could aid in the understanding of when in the life course brain health trajectories begin to diverge in groups with different levels of CVH and when CVH treatment and prevention strategies should be implemented.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature for cognitive and brain structure changes in relation to cardiovascular disease, using traditional sources (e.g., PubMed).
2. **Interpretation**: Our findings indicate that lower adherence to the American Heart Association's "Life's Essential 8" guidelines was associated with a steeper decline in cognition, greater accumulation of white matter hyperintensities, and reduced gray matter volume and hippocampal atrophy over 10 years in late midlife. Taken together, these findings suggest that brain health changes related to CVH can be observed already by midlife and that interventions should target younger ages to reduce the risk for adverse cognitive outcomes in old age.
3. **Future directions**: Future studies with repeatedly measured LE8 are required to evaluate the longitudinal evolution of LE8 or interventions to improve the influence of LE8 scores on brain aging.

2 | METHODS

2.1 | Data availability

Requests for access to the data for this study can be made at the CARDIA website: https://www.cardia.dopm.uab.edu/.

2.2 | Study population

The CARDIA Study is a large prospective cohort study investigating the development of and risk factors for cardiovascular disease.[15] Briefly, starting in 1985, 5115 Black and White community-dwelling adults between 18 and 30 years of age were recruited from population-based samples of four US cities (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California). Within each center, recruitment was balanced by sex, age, and education level. At each examination, participants provided written informed consent, and study protocols were reviewed by institutional review boards at each study site and the CARDIA Coordinating Center; starting in 2020, a single institutional review board at the University of Alabama, Birmingham provided this review.[15]

2.3 | LE8 CVH score

The updated AHA LE8 metric includes healthy diet; participation in physical activity; avoidance of nicotine; healthy sleep; healthy weight; and healthy levels of blood lipids, blood glucose, and blood pressure.[16] Diet was assessed using the interviewer administered CARDIA Diet History.[17] Instead of using the DASH-style (dietary approaches to stop hypertension) diet pattern as proposed by the AHA, the Mediterranean diet (MedDiet) was used as a measure of diet quality, which share similar profiles, with the addition of moderate alcohol use in the MedDiet, which is not recommended in the DASH diet. Moreover, the MedDiet was found to have greater benefits for midlife cognitive performance in the CARDIA population as well as better cognitive outcomes in in other older populations, compared to the DASH diet.[18,19] Physical activity was measured with the CARDIA Physical Activity History questionnaire, which queries the amount of time per week spent in 13 categories of leisure, occupational, and household physical activities over the past 12 months summarized as units of total activity incorporating moderate and high-intensity activities.

Nicotine use was assessed via self-reported question "Have you ever used any tobacco product such as cigarettes, cigars, tobacco pipe, chewing tobacco, snuff, nicotine chewing gum, or a nicotine patch?" If participants answered yes, the answers were further coded into current use, or the most recent past use. Hours of sleep were also ascertained by self-report. BMI was calculated as weight in kilograms divided by height in meters squared. Plasma total and high-density lipoprotein (HDL) cholesterol was measured enzymatically as previously described,[20] and used to estimate non-HDL cholesterol. A digital blood pressure monitor (Omron HEM-907XL; Online Fitness) was used to measure systolic and diastolic blood pressure. Glucose levels were determined through fasting glucose and/or HbA1c.

The detailed definitions and scoring for the component metrics of LE8 are provided in Table S1in supporting information. Each component was scored from 0 to 100 points, with higher scores indicating healthier CVH.[21] The overall LE8 score was calculated as the mean of the 8 metrics, ranging from 0 (lowest) to 100 (highest), and the continuous score was categorized as poor LE8 for scores ranging from 0 to 49, intermediate for scores ranging from 50 to 79, and optimal for scores ranging from 80 to 100 as suggested by the AHA and previous literature.[16,21–24] The individual LE8 components were also categorized according to the same cut-offs.

2.4 | Cognitive function assessment

CARDIA technicians who underwent formal training and certification administered a battery of cognitive tests at the years 25, 30, and 35 visits and included the Digit Symbol Substitution Test (DSST), the Stroop Test, and the Rey Auditory Verbal Learning Test (RAVLT).[25] The DSST, a subtest of the Wechsler Adult Intelligence Scale (3rd edition), assesses most prominently visual motor speed, sustained attention, and working memory. The range of scores is 0 to 133, with higher scores indicating better performance. The Stroop Test evaluates the ability to view complex visual stimuli and to respond to one stimulus dimension while suppressing the response to another dimension, an "executive" skill largely attributed to frontal lobe function.[18] The interference score provides a measure of how much additional executive processing is needed to respond to an incongruent trial; thus, a higher interference score indicates worse performance on the task. The RAVLT assesses the ability to memorize and to retrieve words (verbal memory). Results from the long delay (10 minutes) free recall were used in analyses. The range of scores is 0 to 15, with higher scores indicating better performance. A cognitive composite score was created by summing the *z* scores of each cognitive test. Accelerated decline in cognition was defined as ≥ 1 standard deviation (SD) from the mean decline in the cognitive composite across the 10 years of follow up.

2.5 | Brain MRI measures

Starting at the year 25 visit, a subset of CARDIA participants completed MRI brain scanning at three of the four clinic sites (Birmingham, Alabama; Minneapolis, Minnesota; and Oakland, California) with approximate balance within four strata of race (Black, White) and sex (male/female).[20] The MRI scans were acquired on 3T scanners located at each CARDIA study site: Siemens 3T Tim Trio/VB15 platform in Minneapolis and in Oakland, and Philips 3T Achieva/2.6.3.6 platform in Birmingham. Standard quality assurance protocols using phantoms previously developed for the Functional Bioinformatics Research Network and the Alzheimer's Disease Neuroimaging Initiative were used. Structural images used for this study were acquired with 1 mm isotropic 3D T1 and T2 sequences. Scan acquisition parameters have been previously described,[20] and were processed using previously described methods.[26–28] In brief, structural images were processed using an automated multispectral computer algorithm that classified all supratentorial brain tissue into GM, white matter, and cerebrospinal fluid, and identified anatomic regions of interest (ROIs). After correction of intensity inhomogeneities,[29] a multi-atlas skull stripping algorithm was applied for the removal of extra-cerebral tissues.[30] Each T1-weighted scan was then automatically segmented into a set of anatomical ROIs using a multi-atlas label fusion method.[31] The images were visually checked for incidental findings, motion artifacts, and other quality issues. A multimodal white matter lesion segmentation (WMLS) technique[28,32] was applied using T1, fluid-attenuated inversion recovery, and T2 images to segment WMLs. WMLS is a supervised learning method that trains on lesions manually delineated by an expert radiologist. The lesion segmentation involves data preprocessing via histogram standardization and co-registration, feature extraction, training a voxelwise discriminative model, voxelwise label assignment, and false-positive elimination.

2.6 | Analytic sample

Our sample consists of the 3526 CARDIA participants who attended the year 20 examination, the year all the LE8 exposure components for this study were collected. Further inclusion criteria were to have at least one cognitive test completed at any of the following assessments across 10 years, resulting in an analytical cohort of 3224 participants (309 had missing cognitive assessment), 3201 had all three cognitive assessments, 18 had two, and 5 had only one assessment. The MRI subsample ($n = 1022$) consisted of participants who had at least one MRI examination across the 10 years of follow-up, 334 had all three MRIs, 279 had two MRIs, and 409 had one MRI exam. Compared to the main sample at baseline, the participants of the MRI analytic sample were more likely to be White, have more years of education, and less likely to smoke ($P < 0.001$ for all).

2.7 | Covariates

Demographic characteristics at our analytic baseline (year 20) including age, sex, years of education, and race were based on self-report. Apolipoprotein E (*APOE*) phenotype was determined from plasma samples by a modification of the methods of Kamboh et al.[33] Participants

were classified according to *APOE* phenotype and participants were categorized as having any ε4 versus no ε4 allele.

2.8 | Statistical analysis

Participant characteristics across LE8 groups were compared using the χ^2 tests for categorical variables and one-way analyses of variance for continuous variables.

Linear mixed effects regression was used to examine the association between level and 10-year change in the cognitive measures and (1) our primary predictor, the overall LE8 score as a continuous measure and as categories and (2) the individual LE8 items. The fixed effects of the model included the LE8 score or categories, linear follow-up time (5-year interval, maximum 10 years in total), and their interaction term. Random effects included intercept and slope for time. The models were adjusted for demographic factors (age, sex, race, and education). We used logistic regression to test whether the odds of accelerated decline on the cognitive composite differed by LE8 category.

To test the association between LE8 group and change in GMV and WMHs in the MRI sub-sample, respectively, we used linear mixed effects regression. The fixed effects of the model included the LE8 categories, linear follow-up time, and their interaction term. Random effects included intercept and slope for time. The models were adjusted for demographic factors (age, sex, race, and education), intracranial volume, and scanning site. The same model set-up was used for testing the association between the individual LE8 items and MRI brain measures.

To further explore the moderating associations of sex, race, and *APOE* status, an interaction term for each of these factors with the LE8 categories were entered in the mixed linear effect regression models for each outcome (cognitive and MRI measures). All statistical analyses were performed using Stata SE 17.0 (StataCorp LP).

3 | RESULTS

At baseline, participants' mean age was 45 (range 37–55), 57% ($n = 1841$) were female, and 45% were Black ($n = 1,470$). Only 17.4% of the participants had ideal LE8 scores and 15.0% had poor LE8 scores. The distribution of the LE8 score was largely normal with both the mean and median scores estimated at 65 (interquartile range 55–76). The participants with poor LE8 were more likely to be women, Black, have lower education, and more likely to be an *APOE* ε4 carrier (Table 1).

At baseline, participants in the poor LE8 category performed worse across all tests compared to the ideal category (Table S2 in supporting information and Figure 1). Across 10 years, there was a modest positive association between the LE8 continuous score and DSST (β: 0.059, 95% confidence interval [CI]: 0.003 to 0.010), RAVLT (β: 0.001, 95% CI: 0.001 to 0.002), and the Stroop task (β: 0.004, 95% CI: 0.001 to 0.007). Moreover, the poor LE8 group had significantly steeper decline on the DSST (β: −0.32, 95% CI: −0.50 to −0.15), and the RAVLT (β: −0.06, 95% CI: −0.10 to −0.01), and trend level significance for the Stroop task (β: −0.16, 95% CI: −0.33 to 0.01) compared to the ideal LE8 group. The rate of decline for the intermediate group was not different from the ideal group for any of the cognitive tests (DSST β: −0.03, 95% CI: −0.14 to 0.09; RAVLT β: −0.03, 95% CI: −0.06 to 0.01, and Stroop task: β: 0.04, 95% CI: −0.06 to 0.14; Figure 1). There were no significant interactions between the LE8 score (continuous) and sex, race, or *APOE* ε4 over time for any of the cognitive tests (Table S3 in supporting information). Moreover, the poor LE8 group were twice as likely to have an accelerated decline of ≥ 1 SD in the cognitive composite score over 10 years (odds ratio [OR]: 2.11, 95% CI: 1.20 to 3.72) compared to the ideal group, whereas the intermediate group did not have a significantly higher likelihood of accelerated decline (OR: 1.20, 95% CI: 0.76 to 1.89). The interactions among LE8 category, accelerated cognitive decline (composite score) and race, sex, or *APOE* ε4 were not significant ($P > 0.05$).

Compared to the overall sample, the MRI sub-sample were less likely to be Black and had better levels on the individual LE8 measures including lower systolic blood pressure, lower BMI, and higher total physical exercise (Table S4 in supporting information). Over the 10 year follow-up, higher LE8 score was modestly associated with less accumulation of WMHs (β: −0.002, 95% CI: −0.005 to −0.000), increased GM (β: 0.011, 95% CI: 0.001 to 0.021), and hippocampal volume (β: 0.00010, 95% CI: 0.00002 to 0.00014). Furthermore, the intermediate LE8 group had significantly higher accumulation of WMHs over time (β: 0.050, 95% CI: 0.004 to 0.095), whereas the poor LE8 group had even higher accumulation of WMHs, but that did not reach statistical significance (β: 0.123, 95% CI: −0.013 to 0.260) compared to participants with ideal LE8 (Figure 2). Moreover, belonging to the poor LE8 group was associated with a steeper decline in total GM (β: −0.584, 95% CI: −1.082 to −0.086), as well as significantly steeper decline in hippocampal volume over 10 years (β: −0.005, 95% CI: −0.009 to −0.001), whereas the intermediate LE8 group was not different in rate of change in total GM or hippocampal volume compared to the ideal group (β: −0.122, 95% CI: −0.458 to 0.213 and β: −0.002, 95% CI: −0.004 to 0.001; Figure 2). Interactions between LE8 score and any of the three MRI measures over time by age, race, sex or *APOE* ε4 were not significant (Table S5 in supporting information).

For the individual LE8 items, poor blood pressure, BMI, sleep duration, and fasting glucose were associated with decline on the DSST, compared to ideal scores; poor BMI, blood pressure, and fasting glucose were associated with decline in the RAVLT; and poor blood pressure and fasting glucose were associated with decline in the Stroop test (Figure 3). For the association between the individual LE8 factors and the brain measures, poor diet was associated with the accumulation of WMHs; poor BMI and diet were associated with decline in total GM, whereas intermediate levels of blood lipids were associated with decline in hippocampal volume (Figure 3).

As a sensitivity analysis, we repeated the analyses restricting to those with complete follow-up for the cognitive function and for the MRI measures. The results remained similar (Tables S6 and S7 in supporting information).

TABLE 1 Study population characteristics at baseline by Life's Essential 8 CVH score ($n = 3224$).

Variable Mean (SD) or *N* (%)	Ideal (> 80) *n* = 562 (17.4%)	Intermediate (50–80) *n* = 2179 (67.6%)	Poor (< 50) n = 483 (15.0%)	*P*
Age	45.3 (3.4)	45.1 (3.7)	45.6 (3.7)	0.011
Female sex	376 (66.9)	1154 (53.0)	311 (64.4)	<0.001
Education, years	15.0 (2.2)	13.8 (2.2)	13.2 (2.0)	<0.001
Black race	126 (22.4)	997 (45.8)	347 (71.8)	<0.001
Current smoking	20 (3.6)	403 (18.7)	178 (36.9)	<0.001
MedDiet score	32.1 (7.1)	25.6 (9.1)	20.0 (11.3)	<0.001
Body mass index (kg/m^2)	24.1 (3.3)	29.5 (6.6)	35.5 (7.9)	<0.001
Hours of sleep/night	7.1 (1.0)	6.9 (3.6)	6.4 (4.2)	0.003
Fasting glucose, mg/dL	89.7 (8.6)	96.1 (20.5)	114.3 (44.2)	<0.001
Systolic blood pressure, mm Hg	108.1 (10.0)	116.0 (13.8)	128.1 (18.0)	<0.001
Non-HDL, mg/dL	110.8 (26.1)	133.1 (35.3)	149.2 (41.7)	<0.001
Physical activity score	488.5 (271.3)	338.3 (269.3)	173.6 (190.7)	<0.001
APOE ε4 carrier	128 (25.1)	584 (30.3)	142 (34.1)	0.010

Abbreviations: *APOE*, apolipoprotein E; CVH, cardiovascular health; HDL, high-density lipoprotein; MedDiet, Mediterranean diet; SD standard deviation.

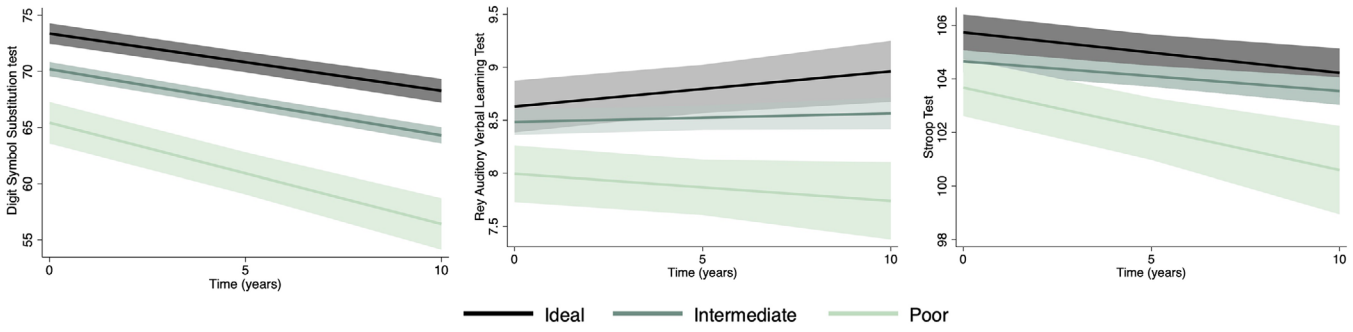

FIGURE 1 Life's Essential 8 risk factors and level and change in cognitive tests over 10 years ($n = 3224$[a]). Adjusted for age, sex, education, and race. Ideal $n = 562$, (17.4%); Intermediate $n = 2179$, (67.6%); $n = 483$, (15.0%). [a]$n = 1322$ had all three cognitive assessments, $n = 1336$ had two, and $n = 548$ had one assessment.

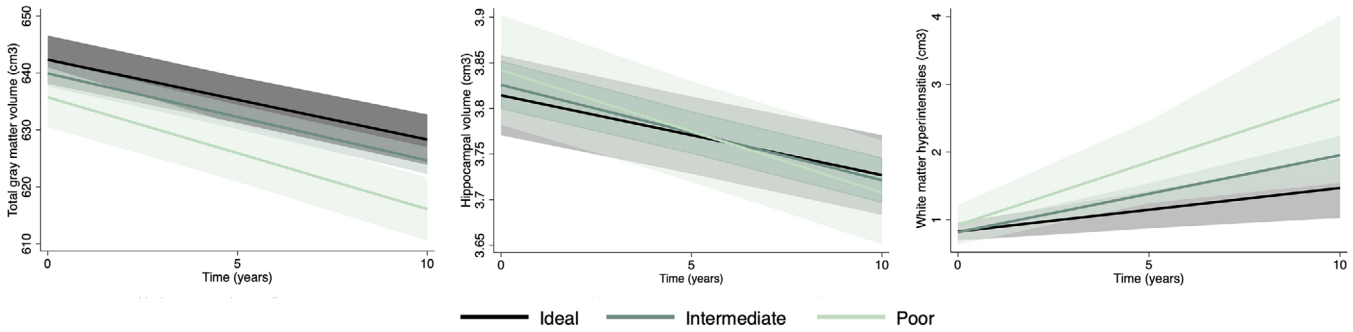

FIGURE 2 Life's Essential 8 risk factors and change in brain measures over 10 years ($n = 1022$[a]). Adjusted for age, sex, education, race, and intracranial volume. Ideal $n = 198$, (19.4%); Intermediate $n = 693$, (67.8); Poor $n = 131$, (12.8%). [a]$n = 334$ had all three MRIs, $n = 279$ had two MRIs, and n = 409 had one MRI exam. MRI, magnetic resonance imaging.

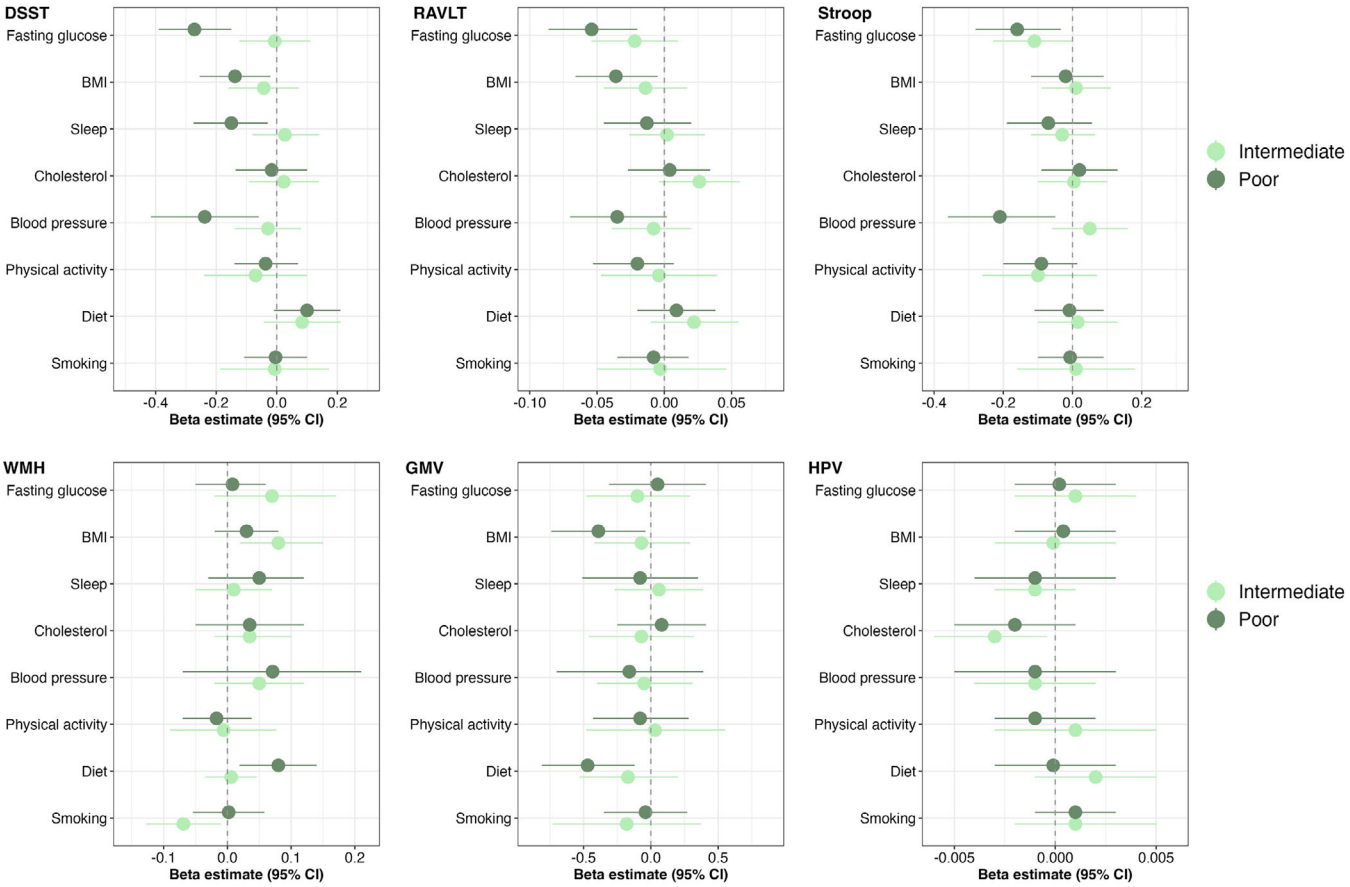

FIGURE 3 The association of individual Life's Essential 8 factor scores and 5-year change in the composite cognitive score and brain measures. Reference group: ideal score of each individual factor. Model adjusted for age, sex, education, race. Models with MRI outcomes were additionally adjusted for intracranial volume. BMI, body mass index; BP, blood pressure; CI, confidence interval; DSST, Digit Symbol Substitution Test; GMV, gray matter volume; HPV, hippocampal volume; MRI, magnetic resonance imaging; RAVLT, Rey Auditory Verbal Learning Test; WMH, white matter hyperintensities.

4 | DISCUSSION

In this study, we examined prospective associations between CVH, as measured by the new AHA LE8 guidelines, and cognitive and brain health trajectories in midlife in a large sample of Black and White adults. Our findings indicate that lower adherence to the LE8 guidelines was associated with a steeper decline in cognition, and with greater emergence of WMHs and reduced GM volume, and hippocampal atrophy over 10 years in late midlife. Taken together, these findings suggest that brain health changes related to CVH can be observed already by midlife and that interventions for CVH should target younger ages to mitigate the risk for adverse cognitive outcomes in old age.

There has been very limited work on the association between CVH and midlife brain health and none to date using the recently developed LE8 scoring system. Our findings provide an important extension to these studies by focusing on the relationship between CVH and cognitive and brain changes earlier in the aging trajectory. Midlife is a sensitive period of life where divergence in cognitive and brain aging may begin as a result of the accumulation of risk factors and subclinical brain changes that may underlie the foundation of future Alzheimer's disease and related dementia (AD/ADRD).[25] Prior findings have shown that accelerated decline in memory performance and hippocampal atrophy coincide around a decade before sporadic dementia onset.[34] Our findings suggest that individuals with poor CVH may experience such decline earlier across several cognitive domains. Indeed, for all cognitive tests, poor scores on the LE8 were associated with lower performance already at baseline, indicating a divergence in cognitive function prior to midlife in those with high CVD burden. In addition, WMHs have been shown be associated with worse working memory in young/middle-aged adults and executive function across adulthood,[35] which may explain the lower scores already at midlife.

Most prior studies that investigated CVH health and cognitive outcomes have been conducted in older adults,[9,10,12] including a recent study that reported that lower LE8 score was associated with increased risk of incident dementia, and more adverse cognitive and neuroimaging outcomes;[36] however, findings have been mixed. Studies with participants in their sixth and seventh decade of life found that vascular risk factors were associated with rate of cognitive decline primarily in processing speed and executive functioning,[37,38] while

in older cohorts there were differences in cognition only at baseline with no associations on subsequent decline in those with higher risk profiles.[39] We found that having a poor LE8 score was associated with lower processing speed (DSST), recall (RAVLT), and executive function (Stroop task) already at baseline and faster decline in processing speed and recall. Taking together the findings in older adults and our findings in midlife, evidence suggests intervening earlier in the life course for CVH might be an optimal strategy for brain health.

Furthermore, higher GM volume, and lower WMHs in relation to better cardiovascular health profiles have been reported in older adults, but most of these were cross-sectional associations, and may therefore limit interpretation. Importantly, WMHs have been found to be predictive of future dementia. A large systematic review found that having WMHs at baseline conferred a 14% greater risk of cognitive impairment and all-cause dementia, 25% greater risk of AD, and 73% greater risk of vascular dementia, while continuously higher volume of WMHs were also related to higher risk.[40] Moreover, we found that poor LE8 in midlife was associated with a faster decline in hippocampal volume, which is an early indication of dementia risk.[41] Our findings underscore that ideal CVH in early midlife could protect future brain health,[9,10,12] and extends prior findings by examining the longitudinal relationship between LE8 and brain health earlier in the aging process. In addition, our findings indicate that midlife poor CVH is associated with both vascular and neurodegenerative processes early in aging, supporting findings in older adults, where these pathologies often co-exist in individuals with high CVH risk.[42] In general, changes in brain structure or lesions occur before noticeable cognitive changes can be observed,[43] which is in line with our findings. For the intermediate LE8, these participants had higher WMHs accumulation but did not show steeper decline in cognition, which may indicate that the brain-related changes have yet to affect cognitive function. This may be an interesting group to follow to understand whether intermediate LE8 will eventually lead to poorer cognition or whether the brain changes associated with intermediate LE8 is below the threshold of significant cognitive decline. Indeed in a previous study, we have shown that the likelihood of accelerated decline increases with the number of cardiovascular risk factors.[44] The poor LE8 group had both worse brain measures as well as faster cognitive decline; hence, we are unable to disentangle which may have occurred first in this cohort. Ideally, studies with younger baseline age would be able to address this. Without known effective cures for ADRD, even modest reductions or delays in cognitive decline, such as those found in this study, can have a significant impact by slowing down dementia-related impairment and disease burden.[2,45]

Moreover, we found that the individual LE8 items had differential relationships with the cognitive assessments and brain measures measures across time. None of the individual measures were associated with all outcomes; however, fasting glucose was associated with accelerated decline in all three cognitive tests, albeit less so than for the overall LE8 score. This indicates that a comprehensive CVH measure such as the LE8 is more sensitive in capturing early decline in cognition and deterioration in brain health than individual CVH measures. This may be particularly important when assessing brain health earlier in the aging process when there may be more variability in the relationship between vascular risk factors and brain cognition due to possible reserve/resilience processes[38] and less accumulated effects, compared to older populations.

The strength of this study includes the population-based design in a large and well-characterized cohort of middle-aged adults that integrated comprehensive LE8 assessments, and longitudinal cognitive and structural brain MRI data, making it possible to assess brain health changes in relation to LE8 profiles from early to late midlife. There are also some limitations to consider in this study. First, the lack of some health factors used in LE8 in CARDIA at follow-up visits hindered the assessment of the associations of longitudinal change in LE8 on brain health. Future studies with repeatedly measured LE8 are required to evaluate the longitudinal evolution of LE8 or interventions to improve the influence of LE8 scores on brain aging. Our findings may not be generalizable to other racial/ethnic groups as our cohort only included Black and White adults. Last, we may have been underpowered in the interaction analyses with age, sex, race, and *APOE* ε4 status, and thus these results were hard to interpret.

In conclusion, this study provides evidence that poor CVH profiles measured by the AHA LE8 metrics were associated with faster progression of brain aging in midlife, including cognitive function as well as neuroimaging markers of atrophy and cerebral small vessel disease. These results indicate a potential beneficial role of promoting CVH as a feasible approach for maintaining brain health, and that such strategies should be implemented at midlife or even earlier.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to report. Author disclosures are available in the supporting information.

CONSTENT STATEMENT

At each examination, participants provided written informed consent, and study protocols were reviewed by institutional review boards at each study site and the CARDIA Coordinating Center; starting in 2020, a single institutional review board at the University of Alabama, Birmingham provided this review.

ORCID

Christina Silvia Dintica https://orcid.org/0000-0001-8186-8140

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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